IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.: 1853
Bennett *et al.*	Art Unit: 1648
Appl. No. 10/622,088	Examiner: Horning, Michelle S.
Filed: July 18, 2003	Atty. Docket: IVGN 332
For: **Viral Vectors Containing Recombination Sites**	

Amendment and Reply Under 37 C.F.R. § 1.111

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In reply to the Office Action dated May 15, 2007, Applicants submit the following Amendment and Remarks.

Amendments begin on page 2 of this paper.

Remarks begin on page 5 of this paper.

It is not believed that extensions of time or fees for net addition of claims are required beyond those that may otherwise be provided for in documents accompanying this paper. However, if additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and any fees required therefore (including fees for the net addition of claims) are hereby authorized to be charged to our Deposit account No. 50-3994.

Amendment to the Specification

In the specification, please replace paragraph [1095] with the following paragraph.

[1095] Use of the best filter set will insure that the optimal regions of the cycle-3 GFP spectra are excited and passed. Suitable filter sets include those designed to detect fluorescence from wild-type GFP (e.g., Omega Optical XF76 filter; Omega Optical Inc., Brattleboro, VT ~~see www.omegafilters.com~~). FITC filter sets may be used to detect cycle-3 GFP fluorescence, but note that these are not optimal and fluorescent signal may be weaker. For example, a FITC filter set may excite cycle-3 GFP with light from 460 to 490 nm, covering the secondary excitation peak and pass light from 515 to 550 nm. A set of this type may allow detection of most but not all of the cycle-3 GFP fluorescence.

Listing of the Claims

This listing of claims will replace all prior versions, and listings of claims in the application.

1-16. (Canceled)

17. (Previously presented) A method of constructing a recombinant virus, comprising:

(a) providing a first nucleic acid molecule comprising all or a portion of at least one viral genome and at least a first and a second recombination site that do not recombine with each other;

(b) contacting the first nucleic acid molecule with a second nucleic acid molecule comprising a sequence of interest flanked by at least a third and a fourth recombination site under conditions such that recombination occurs between the first and third recombination site and between the second and fourth recombination site; and

(c) introducing the nucleic acid molecule of step (b) into a cell that packages the nucleic acid molecule of step (b).

18. (Canceled)

19. (Original) A method according to claim 17, wherein the first nucleic acid molecule comprises all or a portion of at least one retroviral genome.

20. (Canceled)

21. (Canceled)

22. (Original) A method according to claim 17, wherein the first nucleic acid molecule comprises all or a portion of at least one RNA virus genome.

23. (Canceled)

24. (Original) A method according to claim 17, wherein the first nucleic acid molecule is a plasmid or a bacmid comprising an origin of replication and a selectable marker.

25. (Previously presented) A method according to claim 17, wherein the portion of the second nucleic acid between the recombination sites comprises a nucleotide sequence of interest.

26. (Previously presented) A method according to claim 25, wherein the sequence of interest comprises one or more sequences selected from a group consisting of, a sequence encoding one or more polypeptides, a sequence encoding one or more tRNA sequences, a sequence encoding one or more ribozyme sequences, one or more promoter sequences, one or more enhancer sequences, and one or more repressor sequences.

27. (Original) A method according to claim 17, further comprising digesting the first nucleic acid molecule with a restriction enzyme that cleaves the first nucleic acid at a site between the recombination sites.

28-43. (Canceled)

44. (Previously presented) The method of claim 17, wherein the first and second recombination sites are *att*L sites and wherein the third and fourth recombination sites are *att*R sites such that when the first nucleic acid molecule is contacted with the second nucleic acid molecule the first *att*L recombination site recombines with the third *att*R recombination site and the second *att*L recombination site recombines with the fourth *att*R recombination site.

Remarks

Claims 1-16, 18, 20, 21, 23 and 28-43 are canceled. Applicants reserve the right to pursue the subject matter of the original claims in continuing applications. Claims 17, 19, 22, 24-27 and 44 are pending in the application.

I. Drawings

The Examiner has objected to the drawings. (Office Action, page 2.) Applicants thank the Examiner for the courtesy of a phone interview on November 13, 2007. In this interview Examiner Horning confirmed that the objection to the drawings was issued in error and that the formal drawings submitted May 21, 2004 were acceptable.

II. Objections

The Examiner has objected to the inclusion of a hyperlink in the specification. (Office Action, page 3.) Applicants thank the Examiner for pointing out this informality. Paragraph [1095] of the specification is amended herein to replace the hyperlink with a reference to the company name and address.

III. Rejection of the Claims Under 35 U.S.C. § 103(a)

Claims 17, 19-20, 22 and 24-27 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Anderson *et al.* (*Proc. Natl. Acad. Sci. USA 79*:2748-2752 (1982)). (Office Action, page 4.) Applicants respectfully disagree.

The Examiner asserts that Anderson *et al.* "describes a method in which a reaction occurs between a gene of interest and a simian virus 40 plasmid via recombination (whole document, see Abstract)." (Office Action, page 5.) Applicants respectfully assert that Anderson *et al.* does not disclose the use of "recombination sites", as this term is used with respect to the claims presented herein.

Applicants note that in Anderson *et al.*, DNA encoding thymidine kinase was co-transfected with SV40 or pBR322 DNA into mouse cells. Analysis of a recombinant plasmid obtained by plasmid rescue indicated that the thymidine kinase gene had become joined with the SV40 or pBR322 sequences and that a small area of homology may have been involved in the

recombination process. However, the recombination disclosed in Anderson *et al.* is suggested to be "homologous recombination, non-homologous recombination or simple ligation." (See Anderson *et al.* page 2752, first column, lines 5-7.) With respect to speculation regarding molecular events, Anderson *et al.* states "one might envision that the recognition and pairing involves a three-strand mechanism similar to that suggested by Meselson and Radding (35) for homologous recombination." (See Anderson *et al.*, page 2752, first column, lines 51-53.)

A recombination site, as described in the captioned application,

> refers to a recognition sequence on a nucleic acid molecule that participates in an integration/recombination reaction by recombination proteins. Recombination sites are discrete sections or segments of nucleic acid on the participating nucleic acid molecules that are recognized and bound by a site-specific recombination protein during the initial stages of integration or recombination. For example, the recombination site for Cre recombinase is *lox*P, which is a 34 base pair sequence comprised of two 13 base pair inverted repeats (serving as the recombinase binding sites) flanking an 8 base pair core sequence (see FIG. 1 of Sauer, B., *Curr. Opin. Biotech. 5*:521-527 (1994)). Other examples of recombination sites include the *att*B, *att*P, *att*L, and *att*R sequences described in U.S. provisional patent applications 60/136,744, filed May 28, 1999, and 60/188,000, filed Mar. 9, 2000, and in co-pending U.S. patent applications Ser. Nos. 09/517,466 and 09/732,91--all of which are specifically incorporated herein by reference-and mutants, fragments, variants and derivatives thereof, which are recognized by the recombination protein λ Int and by the auxiliary proteins integration host factor (IHF), FIS and excisionase (Xis) (see Landy, *Curr. Opin. Biotech. 3*:699-707 (1993)).

(Specification, paragraph [0163], underlining added.)

Recombination sites are also described in the examples of the captioned application. For example, in Example 1, the vector pAd/CMV/V5-DEST (Figure 6) is described which contains a selectable marker between *att*R1 and *att*R2 recombination sites. A sequence of interest that is flanked by compatible recombination sites *att*L1 and *att*L2 may be inserted into the vector using an LR recombination reaction. Recombination sites described in the captioned application include sites such at *lox* sites or *att* sites and the use of recombination proteins such as Cre or Int.

Applicants further note that the use of *att* recombination sites is specifically recited in claim 44 and the use of *att* recombination sites is not found in Anderson *et al.*[1] Thus, Applicants are confused as to why the Examiner has not indicated that claim 44 is directed to allowable subject matter.

Anderson *et al.* does not disclose the use of recombination sites, as described in the captioned application, in the transformation of mouse cells with the thymidine kinase gene. Further, there is no disclosure in Anderson *et al.* of first and second recombination sites which do not recombine with each other as recited in the claims presented herein. Because the cited reference, Anderson *et al.*, does not disclose all of the limitations of the claims, Applicants respectfully note that the Examiner has failed to establish a *prima facia* case of obviousness.

In view of the above, Applicants respectfully request reconsideration and withdrawal of the rejection of the claims under 35 U.S.C. § 103(a).

IV. Double Patenting

Claims 17 and 44 stand rejected on the ground of non-statutory obviousness type double patenting as being unpatentable over claims 1, 17 and 18 of U.S. Patent No. 7,198,924. (Office Action, page 6.) Applicants defer responding to this ground of rejection until patentable subject matter has been determined, at which time Applicants will consider filing a terminal disclaimer.

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1 While Applicants do not believe it is necessary, Applicants would agree to clarify the subject matter of claim 17 by amending it to recite "site specific" recombination sites. If this would overcome the rejection based on Anderson *et al.*, Applicants request that the Examiner call Applicants' undersigned representative at the number provided below.

Conclusion

Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

/Peter G. Foiles/

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Date: November 15, 2007